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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/080,839	02/22/2002	Paul Schimmel	TSRI 813.1	9625

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OLSON & HIERL, LTD.
36th Floor
20 North Wacker Drive
Chicago, IL 60606

EXAMINER	
KERR, KATHLEEN M	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 05/05/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/080,839	SCHIMMEL ET AL.	
	Examiner	Art Unit	
	Kathleen M Kerr	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *2/6/04*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-28* is/are pending in the application.

4a) Of the above claim(s) *7-23 and 26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,24,25,27 and 28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Application Status

1. In response to the previous Office action, a written restriction requirement (mailed on January 6, 2004), Applicants filed an election received on February 6, 2004. Claims 1-28 are pending in the instant Office action.

Election

2. Applicant's election without traverse of Group I, Claims 1-6, 24, 25, 27, and 28 in a paper received on February 6, 2004 is acknowledged. Claims 7-23 and 26 are withdrawn from further consideration as non-elected inventions. Claims 1-6, 24, 25, 27, and 28 will be examined herein.

Priority

3. The instant application is granted the benefit of priority for the U.S. Provisional Application No. 60/270,951 filed on February 23, 2001 as requested in the declaration and the first lines of the specification.

Information Disclosure Statement

4. No information disclosure statement has been filed with the instant application as of the date mailed of the instant Office action. Applicants are reminded that they have a duty to disclose all information, of which they are aware, relevant to the patentability of the pending claims (see 37 C.F.R. § 1.56 and M.P.E.P. § 2000).

Compliance with the Sequence Rules

5. By virtue of the sequence listing filed on February 22, 2002 with the original application in computer readable form and paper copy, the instant application fully complies with the sequence rules.

Objections to the Specification

6. In the specification, the Abstract is objected to for not completely describing the disclosed subject matter in the appropriate format (see M.P.E.P. § 608.01(b)). The Abstract must be in paragraph form; the Examiner suggests deletion of the disclosure of the sequence in the Abstract. Moreover, it is noted that in many databases and in foreign countries, the Abstract is crucial in defining the disclosed subject matter, thus, its completeness is essential. The Examiner suggests the inclusion of the source species of the full-length tryptophanyl tRNA synthetase, human, as well as the fact that the claimed polypeptide, described as useful as an angiogenesis inhibiting, is a fragment of the known full-length sequence. Correction is required.

7. The specification is objected to for being confusing with respect to the sequence listing. The sequence listing contains 13 sequences. Every SEQ ID NO is mentioned in the specification and/or the claims except SEQ ID NO: 4. It is unclear why said sequences are in the sequence listing if they are not described in the specification. All SEQ ID NOs in the sequence listing must be described in the specification. Appropriate correction or citation of SEQ ID NO:4 in the specification is required.

8. The specification is objected to for not appropriately describing the figures, in their entirety. On pages 6-7, the figures are described. Figures 2 and 5 have panels, i.e., 5A-5D, that must be named, if not individually described, in pages 6-7. Correction is required.

Claim Rejections - 35 U.S.C. § 112

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 1-5, 24, and 27-28 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrase "consisting essentially of" is confusing as it is applied, therein, to a polypeptide sequence. No definition of this transitional phrase as it is applied to polypeptides is found in the specification. However, on page 22, considered part of the invention is derivatives of SEQ ID NO:12, i.e., including alterations within the sequence. This is inconsistent with the accepted definition of "consisting essentially of" as found in M.P.E.P. § 2111.03:

> "A consisting essentially of' claim occupies a middle ground between closed claims that are written in a consisting of' format and fully open claims that are drafted in a comprising' format." PPG Industries v. Guardian Industries, 156 F.3d 1351, 1354, 48 USPQ2d 1351, 1353-54 (Fed. Cir. 1998). See also Atlas Powder v. E.I. duPont de Nemours & Co., 750 F.2d 1569, 224 USPQ 409 (Fed. Cir. 1984); In re Janakirama-Rao, 317 F.2d 951, 137 USPQ 893 (CCPA 1963); Water Technologies Corp. vs. Calco, Ltd., 850 F.2d 660, 7 USPQ2d 1097 (Fed. Cir. 1988)."

Since even the most open language, "comprising" language, with respect to polypeptide sequences is specific for the sequence from end-to-end (i.e., no alterations within SEQ ID

NO:12), a claim that is less open as governed by the "consisting essentially of" language also cannot have changes within the sequence. Since "absent a clear indication in the specification or claims of what the basic and novel characteristics actually are, "consisting essentially of" will be construed as equivalent to "comprising" for purposes of prior art" (see M.P.E.P. § 2111.03). Clarification is required. The Examiner suggests percent identity language if Applicants want to claim some variability **within** the polypeptide.

10. Claims 1-5, 25, and 27-28 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "about", as it attempts to limit the molecular weight of the claimed polypeptide, is unclear as to how much breadth can be allowed. Similar clarity is required for how the term "about" limits protein concentration in a composition (see Claim 25). No description of experimental error for the terms described by the word "about" is noted such that one of skill in the art could ascertain the metes and bounds with any certainty. In Figure 1, sizes of 53, 48, 46, and 43 kilodaltons are described. Is anything "about 45 kD" if it is less than 48 kD? The percentage of breadth for the term "about" is unclear as no ± indication of molecular weights or protein concentration is disclosed in the specification. Clarification is required.

11. Claims 7 and 25 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The transitional phrase "having" or "has" is unclear as to its meaning, whether it is open or closed. As noted in M.P.E.P. § 2111.03, the transitional phrase

"having" or "has" must be interpreted in light of the specification. Due to the confusing nature of the specification's including several fragments of a known, full-length protein, the metes and bounds of the term "having" or "has" are not clearly presented. If the phrase is meant to close the claim, the Examiner suggests ---consisting of---. If the phrase is meant to be open, the Examiner suggests ---comprising---. For purposes of prior art, the instant claim will be given its broadest reasonable interpretation, which is open.

12. Claims 27-28 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrase "sufficient for at least a single dosage of administration" is unclear as to its quantity. On page 35, doses are described as at least about 10mg/kg body weight. In the examples, 0.1 mg/ml-0.5 mg/ml solutions are used (see page 42). Thus, the quantity of polypeptide required for the kit is unclear.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

13. Claim 5 is rejected under 35 U.S.C. § 112, first paragraph, written description, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the

claimed invention. The instant claim is drawn to an anti-angiogenesis fragment of SEQ ID NO:12 of less than 43 kD.

Although the genus of such small fragments is discussed in the specification, there is no evidence that any representative species of such a genus was in the possession of the inventors at the time of filing. To satisfy the written description aspect of 35 U.S.C. § 112, first paragraph, for a claimed genus of molecules, it must be clear that: (1) the identifying characteristics of the claimed molecules have been disclosed, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these; and (2) a representative number of species within the genus must be disclosed.

The specification does not disclose any representative species of any of the recited polypeptide, specifically being less than 43 kD, since the only fragment disclosed with evidenced function (also being a requirement in the claim) even close to the size limitation is the T2 cleavage product that is 43 kD, not *less than* 43 kD. Therefore, claim 5, as written, fails to satisfy the written description requirement.

Claim Rejections - 35 U.S.C. § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

14. Claims 1-4 are rejected under 35 U.S.C. § 102(b) as being anticipated by Tolstrup *et al.* (Transcriptional Regulation of the Interferon-γ-inducible Tryptophanyl-tRNA Synthetase Includes Alterative Splicing. J. Biol. Chem. (1995) 270(1): 397-403). The instant claims are drawn to an anti-angiogenesis fragment of human tryptophanyl-tRNA synthetase wherein said fragment inhibits ocular neovascularization and contains the sequence ---HVGH--- having a molecular weight of about 45 kD.

Tolstrup *et al.* teach the polypeptide known as "mini TrpRS" in the instant specification; mini TrpRS is a 48 kD protein starting from methionine 48 (see Abstract). Said polypeptide is anti-angiogenic (also called angiostatic, see Figure 1 of instant specification) and is about 45 kD, having a particular weight of 48 kD (± <10%). Said polypeptide is also effective at ocular neovascularization (see Figure 3 of the instant specification).

15. Claims 1-6, 24, and 25 are rejected under 35 U.S.C. § 102(e) as being anticipated by Schimmel *et al.* (WO 01/74841 with an earliest effective U.S. filing date of March 31, 2000).

The applied reference has common inventors with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. § 102(e). This rejection under 35 U.S.C. § 102(e) might be overcome either by a showing under 37 C.F.R. § 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 C.F.R. § 1.131.

Schimmel *et al.* teach human full-length TrpRS and mini-TrpRS, the 49 kD fragment taught by Tolstrup *et al.* as noted in Figure 1 of the instant specification. Schimmel *et al.* also teach elastase-produced fragments of 47 kD (supermini TrpRS) and 44 kD (inactive TrpRS) and

their his-tagged forms for easy purification (see page 55 of the priority document). While Schimmel *et al.* do not teach the 44kD fragment as having anti-angiogenesis activity, this feature is inherent in the structure of the polypeptide, which is the same as SEQ ID NO:12 disclosed in the instant application.

Claim Rejections - 35 U.S.C. § 103

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

16. Claim 6 is rejected under 35 U.S.C. § 103(a) as being unpatentable over Frolova *et al.* (Cloning and nucleotide sequence of the structural gene encoding for human tryptophanyl-tRNA synthetase. Gene (1991) 109(2): 291-296) in view of Kisselev (Mammalian tryptophanyl-tRNA synthetases. Biochimie (1993) 75(12): 1027-1039) and Jones *et al.* (Current trends in molecular recognition and bioseparation. J. of Chromatography (1995) 707: 3-22). The instant claim is drawn to a polypeptide comprising a C-terminally-his-tagged fragment of full-length tryptophanyl-tRNA synthetase (SEQ ID NO:7, which is a his-tagged SEQ ID NO:12).

Frolova *et al.* teach the DNA sequence encoding tryptophanyl-tRNA synthetase (TrpRS), a polypeptide comprising SEQ ID NO:12, a fragment of tRS. Frolova *et al.* do not teach purification of the encoded protein by any means.

Kisselev teaches antibody reactivity and non-canonical functions of TrpRS, but do not expressly teach purification of human TrpRS to facilitate the study of either.

Jones *et al.* teach methods of protein purification, particularly C-terminal hexa-histidine tags on proteins (see pages 14-15).

At the time of the invention, it would have been obvious to one of ordinary skill in the art to use the DNA sequence taught by Frolova *et al.* and express it as a C-terminally hexahistidine tagged protein for purification because further studies on the activities of human TrpRS are clearly warranted as noted by Kisselev, said studies being facilitated by reactive antibodies whose production would require purified protein. One would have been motivated to produce such a protein to provide a pure protein for further interferon-related studies as well as to make antibodies. One would have had a reasonable expectation of success due to the extensive recombinant DNA technologies available for the manipulation of DNA to produce a purified protein when an encoding sequence is available, like that of Frolova *et al.*

Other Art of Relevance

17. The following references are noted to complete the record:

a) Epely *et al.* (Limited Proteolysis of Tryptophanyl-tRNA Synthetase from Beef Pancreas. Eur. J. Biochem. (1975) 61:139-146) teaches elastase treatment of bovine TrpRS and, thus, an analogous fragment of TrpRS (T2). The bovine sequence and human sequence are virtually identical over the length of SEQ ID NO:12.

b) Xu *et al.* (High-level expression and single-step purification of human tryptophanyl-tRNA synthetase. Protein Expr Purif. (Nov. 2001) 23(2): 296-300) teach human TrpRS with a C-terminal His_6 tag (see Abstract); this is not available as prior art. If it were available, it would anticipate Claim 6; moreover, no rejections under 35 U.S.C. § 103(a) would have been necessary for Claim 6.

Conclusion

18. Claims 1-6, 24, 25, 27, and 28 are not allowed for the reasons identified in the numbered sections of this Office action. Applicants must respond to the objections/rejections in each of the numbered sections in this Office action to be fully responsive in prosecution.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kathleen M Kerr whose telephone number is (571) 272-0931. The examiner can normally be reached on Monday through Friday, from 9:00am to 6pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathupura Achutamurthy can be reached on (571) 272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Kathleen M Kerr
Examiner
Art Unit 1652

April 29, 2004